# FDA Briefing Document
# Vaccines and Related Biological Products Advisory Committee Meeting
# May 12, 2015

# Licensure of Ebola Vaccines:
# Demonstration of Effectiveness

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## 1.0 Introduction

The Ebola outbreak of 2014 and 2015 in West Africa has caused more than 25,000 cases of Ebola virus disease (EVD) and claimed the lives of more than 10,000 people. Vaccines to protect against EVD are needed to protect people from the current and future outbreaks. Several EVD candidate vaccines have been tested in phase 1 clinical trials, and larger randomized, controlled trials to demonstrate that these vaccines prevent EVD are planned or ongoing. While the recent decline in EVD incidence in affected regions in West Africa is welcome news from a public health perspective, it hampers direct assessment of vaccine effectiveness based on EVD clinical endpoint studies. In addition, other candidate vaccines under development, which are not currently being evaluated in these trials, will need to be evaluated for effectiveness. Although randomized controlled trials (RCTs) using disease endpoints are acknowledged as the most robust study design for demonstrating vaccine efficacy, other approaches to demonstrate Ebola vaccine effectiveness are available and are being considered by the FDA to enable licensure of Ebola vaccines. FDA is working closely with manufacturers interested in developing Ebola vaccines to determine the appropriate licensure path and to plan clinical development.

The topic of the May 12, 2015, Vaccines and Related Biological Products Advisory Committee meeting is to discuss the types of data that can be used to demonstrate effectiveness in the context of pathways to licensure of Ebola vaccines and, if required, what studies should be conducted post-licensure to verify the clinical benefit.

## 2.0 Background

### *2.1 Ebola virus disease and epidemic of 2014 - 15*

Ebola virus disease is a rare and deadly disease in humans and nonhuman primates caused by infection with a virus belonging to the Filoviridae family, genus *Ebolavirus*. Four of the five known Ebola virus species can cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). The fifth, Reston virus (*Reston ebolavirus*), can cause disease in nonhuman primates, but has not been shown to cause disease in humans.

Symptoms of EVD include fever, severe headache, muscle pain, weakness, fatigue, diarrhea, vomiting, abdominal pain and hemorrhage. Symptoms may appear anywhere from 2 to 21 days after exposure to Ebola, but the average is 8 to 10 days (1).

EVD was first described in 1976 near the Ebola River in what is now the Democratic Republic of the Congo. Since then, outbreaks have appeared sporadically in Africa. The natural host of Ebola virus is not known; however, it is thought that bats are the most likely reservoir.

The 2014 - 15 EVD epidemic affecting multiple countries in West Africa is the most widespread Ebola epidemic in history causing significant mortality. According to the WHO, as

of April 7, 2015, the total number of Ebola cases was 25,532 with 10,584 deaths (1). Of these, 9,862 cases (4,408 deaths) occurred in Liberia, 12,155 (3,841 deaths) in Sierra Leone and 3,515 (2,335 deaths) in Guinea. However, in these countries, after early high transmission levels, new infection rates have been significantly reduced. A total of 30 confirmed cases of EVD were reported in the week to 5 April. This is the lowest weekly total since the third week of May 2014. Case incidence in Guinea decreased to 21, compared with 57 confirmed cases the previous week. Liberia reported no confirmed cases. Sierra Leone reported a fifth consecutive weekly decrease from 25 confirmed cases in the week to 29 March to 9 in the week to 5 April (2).

### *2.2 Ebola candidate vaccines*

Three Ebola candidate vaccines are currently in advanced clinical development:

a) An Ebola Virus Recombinant Vesicular Stomatitis Virus-Vectored (rVSV-ZEBOV) vaccine based on a genetically modified vesicular stomatitis virus (VSV) expressing the envelope glycoprotein (GP) from the Ebola Zaire Kikwit strain. The vaccine was developed by the Public Health Agency of Canada (PHAC), and commercial rights were licensed to NewLink Genetics Corp. (Newlink) of Ames, Iowa. Recently, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, U.S.A. (Merck) and NewLink entered into an exclusive licensing and collaboration agreement under which (Merck) was granted exclusive rights to the rVSV-ZEBOV vaccine candidate as well as any follow-on products.

b) A recombinant-replication-deficient chimpanzee Adenovirus Type 3 Vectored vaccine expressing the wild-type GP from the Ebola Zaire strain (ChAd3-EBO-Z). This vaccine has been developed by the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (VRC/NIAID ) using the ReiThera (formerly known as Okairos) adenovirus vaccine platform technology, which was acquired by GlaxoSmithKline Biologicals (GSK) in May 2013.

c) A replication-defective adenovirus serotype 26 (Ad26) vaccine expressing the full-length GP of the Ebola Zaire Virus (Ad26.ZEBOV) developed by Crucell Holland B.V., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, administered in a prime-boost regimen with multivalent Modified Vaccinia Ankara (MVA) - Bavarian Nordic (BN) vaccine, MVA-mBN226B (or MVA-BN-Filo), which expresses the SUDV GP, the EBOVGP, the MARV Musoke GP, and the Tai Forest virus (TAFV) nucleoprotein (NP).

Additional Ebola candidate vaccines are being developed based on different platforms and techniques and first-in-human clinical trials with some of these investigational vaccines are being planned or have been initiated.

### *2.3 Clinical trials with Ebola candidate vaccines*

The safety and immunogenicity of the ChAd3-EBO-Z, the rVSV-ZEBOV and the Ad26.ZEBOV/MVA-mBN226B vaccines have been evaluated in multiple Phase 1 clinical trials

in the United States, Europe and West Africa. Preliminary data derived from these studies suggest that after completion of the proposed vaccination series, these vaccines are immunogenic and do not present safety concerns that would prevent their evaluation in larger Phase 2 and Phase 3 clinical trials.

The US government is sponsoring two large Phase 3 clinical studies to evaluate the safety and efficacy of these vaccines in EVD outbreak areas in West Africa. The NIAID is partnering with the Liberia College of Physicians and Surgeons and the Liberian Institute for Biomedical Research, to conduct a study in Liberia that began early February 2015. The study is called Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) and is a Phase 2/3 clinical trial with planned enrollment of 27,000 subjects designed to evaluate the safety and efficacy of two investigational vaccines intended to prevent Ebola virus infection: the ChAd3-EBO-Z investigational Ebola vaccine and the rVSV-ZEBOV investigational Ebola vaccine (3). The Centers for Disease Control and Prevention (CDC) are working together with the Sierra Leone College of Medicine and Allied Health Sciences (COMAHS), and the Sierra Leone Ministry of Health and Sanitation (MoHS) to conduct a study in Sierra Leone that started in early April 2015. This phase 3 study is called the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE). It is an event-driven, unblinded, randomized, phased introduction vaccine trial to assess the safety and efficacy of the rVSV-ZEBOV candidate Ebola vaccine among approximately 6,000 health care and other frontline workers (4). Both studies are designed to assess vaccine efficacy based on clinical disease endpoints, and serum samples will be collected for immunogenicity analysis. In addition to the 2 large Phase 3 trials sponsored by the US government, the World Health Organization (WHO) is sponsoring a ring vaccination trial in Guinea using the rVSV-ZEBOV vaccine (5).

## 3.0 Workshop: “Immunology of protection from Ebola Virus infection”

A workshop co-sponsored by the US government to discuss important aspects of EVD and vaccine immunology to inform future clinical, scientific and regulatory decision-making related to vaccines to prevent EVD, was held December 2014 (6). The following scientific conclusions were derived from this workshop and are important for considerations on how to demonstrate effectiveness of investigational Ebola vaccines: a) If low Ebola virus attack rates or other factors lead to inconclusive results from phase 3 clinical trials, other approaches to demonstration of effectiveness for licensure may need to be considered; b) Preliminary results in human trials of Ebola vaccines suggest that vaccines are capable of inducing human immune responses at levels comparable to protective responses in non-human primates (NHP); c) NHP studies are important for studying mechanisms of protection and to mimic human infections in important aspects, although vaccine doses required to induce comparable immune responses and protection may differ between humans and NHPs; d) It may be possible to define immune markers that predict protection even in the absence of a complete understanding of the mechanism of protection; e)

Immune markers of protection (including antibody threshold levels) may be different for different vaccines. The importance of assay validation and opportunities for standardization were also discussed.

## 4.0 Non-human primate challenge/protection studies

The majority of vaccine platform approaches that have been developed against ebolaviruses are based on generating immune responses against the Ebola virus GP, and data from several candidate vaccine studies in non-human primates (NHP) were presented and discussed at the workshop.

In one study, Vesicular Stomatitis Virus (VSV)-vectored Ebola vaccines were used to immunize Cynomolgus macaques (*Macaca fascicularis*) followed by challenge with 1,000 pfu of Ebola Zaire. Although surviving and non-surviving NHP differed in their pre-challenge anti-Ebola GP ELISA titers, there was a correlation between survival and levels of total IgG specific to Ebola Zaire GP (7). Protection was achieved in 4/4 vaccinated animals with antibody titer from 1:100 to 1:1,000 (8). However, neutralizing antibody was not consistently detected after immunization, suggesting that neutralizing antibody may not predict protection for this particular vaccine. Likewise, it has not been possible to correlate available measures of cell-mediated immunity (CMI) with protection using VSV-vectored vaccines (8, 9). Some recent studies suggest that innate responses may play a role in VSV-vectored vaccine-induced protection (7, 10).

In challenge studies evaluating human Adenovirus (Ad) type 5-vectored vaccines in NHP, complete protection (100% survival) was observed when challenged animals had pre-challenge GP ELISA titers >1:3,700; 85% survival correlated with an antibody titer of >~1:1,500 (11). For this candidate vaccine, protection did not appear to be mediated solely through antibodies, as animals depleted of CD8+ T cells were not protected and passive transfer of hyperimmune sera failed to protect non-vaccinated animals from challenge (12). Further studies suggested the importance of an effective T cell response for protection. Importantly, immune responses induced after a first dose of Ad5-vectored vaccine reduced both the humoral and cellular immune responses to a second dose of the same vaccine (13), with implications for the utility of Ad-vectored vaccines in populations with high incidence of natural immunity to these vectors.

Complete protection of NHP was also reported using a Chimpanzee Adenovirus 3 (ChAd3)-vectored vaccine at a dose of $10^{10}$ virus particles. At this dose, strong cellular immune responses were detectable (14), again suggesting that for adenovirus-vectored vaccines, in contrast to VSV-vectored vaccines, a cellular immune response may be associated with protection. Other studies reported that greatly improved immune responses and durability of

protection could be achieved by prime – boost immunization strategies using Ad-vectored vaccines (e.g., Ad5, Ad26, or ChAd3) in various combinations with other Ad-vectored vaccines (i.e., Ad26 or Ad35) (13) or with MVA-vectored vaccines (14, 15). The interval between these doses is likely to be important.

Taken together, the data suggest that NHP models, in particular macaque models, mimic human infections and that protective immunity defined in these models may be important for understanding the protective response to vaccination in humans.

## 5.0 Preliminary immunogenicity data from Phase 1 clinical studies

Published immunogenicity data from phase 1 clinical trials are summarized below. Note that the ELISA assays used in these studies were not standardized and that the GMTs were calculated differently. Thus, results are not comparable across studies. The purpose of showing these data is to illustrate that the vaccines evaluated in these studies were immunogenic.

### *5.1 rVSV-ZEBOV Ebola vaccine*

Preliminary data derived from phase 1 studies of VSV-vectored vaccine expressing Ebola Zaire GP showed median GP ELISA antibody responses of ~1:2,000 at day 28 at a vaccine dose of $10^6$ pfu (16). Data from two recently published phase 1 studies conducted at WRAIR and NIH in 40 subjects who received a single intramuscular (IM) dose of either $3x10^6$ or $2x10^7$ pfu showed that all subjects seroconverted as measured by Zaire-Kikwit strain GP ELISA by Day 28 post-vaccination. The GMT was higher in subjects who received the $2x10^7$ pfu dose compared with those who received $3x10^6$ pfu (4079 vs. 1300; see Table 1 of this briefing document) (17). However, when measured by GP ELISA using a heterologous Zaire-Mayinga strain, the highest GMT ($2x10^7$ pfu) was only 1429 (data not shown).

Additional recent phase 1 studies conducted in Europe and Africa evaluated doses from $3x10^5$ to $5x10^7$ pfu administered as a single intramuscular dose (18). GMTs and seroresponse rates observed at day 28 post-vaccination across study sites (Switzerland, Gabon and Germany) are summarized in Table 1 of this briefing document. GP ELISA GMT's ranged from 1056 ($3x10^5$ pfu dose) to 1970 ($2x10^7$ pfu dose), though there was no clear dose-response relationship for GMTs or seroresponse rates across doses and study sites. The published phase 1 studies (17, 18) all evaluated GP ELISA levels using the homologous Zaire-Kikwit glycoprotein and the USAMRIID protocol. Studies to evaluate immune responses to even lower doses of the VSV-vectored vaccine are in progress.

**Table 1. Immune Responses to the rVSV-ZEBOV Vaccine in Healthy Adults ≥ 18 Years of Age as Measured by Homologous Zaire-Kikwit Strain Glycoprotein ELISA at 28 Days Post-Vaccination**

| Study Design | Location | Dose (pfu) | N | GMT[1] | Seroresponse rate[2] n (%) |
|---|---|---|---|---|---|
| Double-blind, placebo-controlled, dose-escalation, Phase 1 studies[3] | Washington DC/ Baltimore | 0 (Placebo) | 12 | 35 | NA[4] |
| | | $3 \times 10^6$ | 20 | 1300 | NA |
| Regules *et al* (17) | | $2 \times 10^7$ | 20 | 4079 | NA |
| Double-blind, randomized, placebo-controlled Phase 1 | Geneva, Switzerland | 0 (Placebo) | 8 | 25 | 0 (0) |
| | | $1 \times 10^7$ | 34 | 1064 | 33 (97.1) |
| Anandji *et al* (18) | | $5 \times 10^7$ | 13 | 1780 | 13 (100) |
| Open-label, uncontrolled, dose-escalation Phase 1 study | Lambaréné, Gabon | $3 \times 10^5$ | 20 | 1056 | 16 (84) |
| | | $3 \times 10^6$ | 4 | 1600 | 4 (100) |
| Anandji *et al* (18) | | | | | |
| Open-label, uncontrolled, dose-escalation Phase 1 study | Hamburg, Germany | $3 \times 10^6$ | 10 | 1393 | 10 (100) |
| | | $2 \times 10^7$ | 10 | 1970 | 10 (100) |
| Anandji *et al* (18) | | | | | |

[1]Results should not be compared across studies as assays used were not standardized [2]Seroresponse was defined as ≥4-fold rise in endpoint titer over baseline. [3]Contains pooled data from two studies. [4]NA=not available. Source: Adapted from Table S1, Supplementary Appendix (17) and Table S6, Supplementary Appendix (18).

### *5.2 ChAd3 vectored Ebola vaccines*

Recently published results of an NIAID-sponsored phase 1 study of a bivalent ChAd3-vectored vaccine expressing Ebola Zaire and Sudan GPs (19) showed that the strongest antibody response as measured by homologous Zaire-Mayinga strain GP ELISA (NIH) was induced at the highest dose of vaccine ($2 \times 10^{11}$ PU), with a GMT of 2,037 at day 28 (See Table 2 of this briefing document). Immune responses at this dose were roughly comparable to those measured with the same assays following vaccination of NHPs with $10^{10}$ PU of the ChAd3-vectored vaccine in previous studies. While CD8+ T-cell responses as measured by intracellular cytokine staining (ICS) were comparable following $2 \times 10^{10}$ and $2 \times 10^{11}$ PU of the ChAd3-vectored vaccine, $2 \times 10^{11}$ PU was required for consistent CD4+ T-cell responses. Preliminary data from a phase 1 study conducted at the Jenner Institute of Oxford University also showed that antibody or CMI responses induced by up to $5 \times 10^{10}$ PU of monovalent ChAd3-vectored vaccine expressing Zaire GP alone were lower than those observed in NHPs protected from challenge (20). However, preliminary data show that boosting of these responses with a multivalent modified vaccinia virus Ankara (MVA)-vectored vaccine at an interval of 3-10 weeks (mean of 6 weeks) could yield further improvement of both humoral and CMI responses (21). Additional

studies, including ChAd3-vectored vaccine boosting of individuals previously primed with an Ebola DNA vaccine, are underway or planned.

**Table 2. Immune Responses to ChAd3-Vectored Ebola Vaccines in Healthy Adults ≥ 18 Years of Age as Measured by Homologous Zaire-Mayinga Strain Glycoprotein ELISA and Intracellular Cytokine Staining (ICS) at 28 Days Post-Vaccination**

| Vaccine[1] and Dose | N | ELISA GMT | Seroresponse[2] rate, n/N (%) | CD4+ response[3] rate, n/N (%) | CD8+ response[3] rate, n/N (%) |
|---|---|---|---|---|---|
| ChAd3-EBO 2 x $10^{10}$ PU | 10 | 331 | 9/10 (90) | 3/10 (30) | 2/10 (20) |
| ChAd3-EBO 2 x $10^{11}$ PU | 10 | 2037 | 10/10 (100) | 10/10 (100) | 7/10 (70) |
| ChAd3-EBO-Z 1 x $10^{10}$ PU | 19 | 235 | NA[4] | 5/10 (50) | 2/10 (20) |
| ChAd3-EBO-Z 2.5 x $10^{10}$ PU | 20 | 402 | NA | 10/14 (71) | 9/14 (64) |
| ChAd3-EBO-Z 5 x $10^{10}$ PU | 19 | 469 | NA | 12/13 (92) | 7/13 (54) |

[1]ChAd3-EBO: bivalent vaccine expressing Zaire and Sudan glycoproteins; ChAd3-EBO-Z: monovalent vaccine expressing Zaire glycoprotein. [2]Seroresponse was defined as statistically significant ($p<0.05$) increase over baseline titer. [3]ICS response was defined as detectable expression of interferon-gamma, interleukin-2, or tumor necrosis factor-alpha following glycoprotein peptide stimulation. [4]NA: not available. Source: Adapted from Table 2 (19) and Figure 3 and text (20).

## 6.0 Demonstration of effectiveness of Ebola vaccine candidates

An application for licensure of an Ebola vaccine must include chemistry, manufacturing and controls information and data to demonstrate the safety and effectiveness of the vaccine. Under FDA's "traditional approval" pathway a demonstration of vaccine effectiveness is based on a clinical disease endpoint or alternatively, an accepted correlate of protection (e.g. antibody response data). Of note, in the case of EVD there is no accepted correlate of protection. Thus, absent the identification of an accepted correlate of protection from, for example, ongoing studies, a demonstration of effectiveness based on a clinical disease endpoint would currently be required for traditional approval. The significant decline in Ebola infection rates may not permit direct assessment of efficacy in currently ongoing clinical disease endpoint trials in West Africa, raising concern that approval using the traditional approval pathway may not be possible. However, there are other pathways to licensure that do not require a demonstration of effectiveness in a clinical disease endpoint trial or an accepted correlate of protection.

In the US, products for serious or life-threatening illnesses providing meaningful benefit over existing treatment can be approved under the accelerated approval provisions (21 CFR 601.40/41) (22). For an Ebola vaccine, approval under these provisions would be based on adequate and well-controlled clinical trials establishing an effect of the product on a surrogate endpoint (e.g., immune response) that is *reasonably likely* to predict clinical benefit. The surrogate endpoint used to evaluate effectiveness could be derived from human studies (e.g.,

immune responses in vaccinated individuals participating in currently planned or ongoing Phase 2 and 3 studies and/or from a comparison of antibody responses in protected vaccinees to those of vaccinees who contract EVD). Under this scenario, ELISA titers achieved in vaccinated NHP that correlate with protection from challenge also could help determine an immunogenicity endpoint reasonably likely to predict protection in humans. Adequate and well-controlled studies would be required post-licensure to verify and describe the clinical benefit of the vaccine.

Approval under the "animal rule" ( 21 CFR 601.90/91/92) may be considered for products for certain serious or life-threatening conditions when definitive human efficacy studies are not ethical or feasible and when other efficacy standards (e.g. the accelerated approval provisions) cannot be used (22). This regulation permits FDA to license vaccines based on adequate and well controlled animal studies when the results of those animal studies establish that the vaccine is *reasonably likely* to produce clinical benefit in humans, provided that safety in humans has been established. There are other regulatory requirements under this provision including criteria for the animal model(s) and the need for data or information, in animals and humans, to allow selection of an effective dose in humans. Post-marketing studies to verify the product's clinical benefit and to further assess safety must be conducted at a time when such studies are feasible and ethical.

Preliminary data presented at a December 12, 2014, US government-sponsored workshop indicated that vaccinated humans may achieve immune responses comparable in magnitude to those associated with protection in NHPs, suggesting the feasibility of an immunogenicity-based approval, although the thresholds associated with protection may differ for each vaccine candidate (6).

## 7.0 Postmarketing studies

Approval under the accelerated approval or "animal rule" provisions would require post-licensure clinical studies to be conducted either during the current or a future EVD outbreak. In the case of accelerated approval, these must be adequate and well-controlled studies designed to verify and describe the clinical benefit, while for the animal rule the post-licensure study requirement can be satisfied with studies, such as field studies, to verify and describe clinical benefit and to assess safety. While randomized, placebo-controlled clinical trials would provide the most definitive confirmatory evidence of vaccine effectiveness, it may become increasingly difficult to conduct such studies.

Given the high case-fatality rate associated with EVD, placebo-controlled trials in a post-licensure setting may be considered unethical, because equipoise (genuine uncertainty in the expert medical community over whether the vaccine will be beneficial) would no longer exist. A number of alternative study designs to evaluate vaccine effectiveness could be considered in this

setting, including step-wedge randomized trials and test-negative case control studies. Step-wedge randomized trials involve the sequential roll-out of the vaccine to participants (individuals or clusters) over a number of time periods. These studies may be considered ethical because, for logistical reasons, it is impossible to have vaccine available simultaneously for all subjects. However, by the end of the study, all participants will have received the vaccine, though the order in which participants receive the vaccine is determined at random. Estimates of vaccine effectiveness take advantage of the differential follow-up time that subjects are at risk of contracting EVD.

In a test-negative study, patients seeking health care for symptoms compatible with EVD are recruited into the study and tested for the disease. Vaccine effectiveness is then estimated as one minus the ratio of the odds of vaccination in subjects testing positive for Ebola to the odds of vaccination in subjects testing negative. Many sources of bias are minimized in this design because cases and non-cases appear similar in all respects, except for the presence of Ebola virus by testing. Such designs have been used by CDC to provide yearly estimates of seasonal influenza vaccine effectiveness (23).

## 8.0 Summary

Approval of Ebola vaccines will be based on data demonstrating the safety and effectiveness of the vaccines. Potential pathways to licensure under consideration include: a) “traditional approval” based on clinical end-point efficacy data, b) accelerated approval, and c) approval under the “animal rule.” Immunological data, collected in ongoing and planned studies, will play an important role in Ebola vaccine evaluation. For example, for the “traditional approval” pathway such data facilitate bridging to populations that were not included in the efficacy trail. For accelerated approval and “animal rule” pathways human immunogenicity data are critical for a demonstration of Ebola vaccine effectiveness.

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